

### **REMARKS**

Reconsideration of this application is respectfully requested.

Claims 75-90 were previously pending. Of these, claims 75 and 88-90 have been amended above. No other claims have been amended, added or canceled by this paper. Accordingly, as amended above, claims 75-90 are presented for further examination.

### **Claim Amendments**

In a sincere effort to define their invention more clearly, Applicants have amended claims 75 and 88-90 above. In claim 75, which is independent, the word "acid" has been inserted in the third line of the claim after the phrase "different non-nucleic." By so doing, Applicants have corrected a possible antecedence problem in the recitation that later follows in claim 75 (" . . . wherein one of said non-nucleic acid components has a tropism for said cell line and the other non-nucleic acid component has a tropism for a target cell . . .").

In each of claims 88-90, the term "native" has been replaced with -- tropism -- . Thus, claim 88 recites "[t]he packaging cell line of claim 75, wherein said nucleic acid component comprises sequences derived from a virus that has a tropism to said cell line." Claim 89 also depends from claim 75 and it recites "wherein said nucleic acid component comprises sequences derived from a virus that has a tropism to said target cell." Finally, claim 90, also dependent from claim 75, now recites "wherein said nucleic acid component comprises sequences derived from a virus that has a tropism to said cell line and sequences derived from a different virus that has a tropism to said target cell."

It is believed that the subject matter of amended claims 75 and 88-90 is fully supported by Applicants' originally filed disclosure. In particular, the term "tropism" is contained variously in the original specification. See, for example, page 31, second paragraph ("This invention overcomes this limitation in the prior art by providing compositions and methods of use for novel virus vectors and for their production wherein such vectors contain at least two surface components that can confer tropism both for target cells and for packaging cells."). Entry of the above claim amendments is respectfully requested.

#### **The Rejection Under 35 U.S.C. §102**

Claims 75-82, 88-89, and 90 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Finer et al., U.S. Patent No. 5,686,279, or Bodner et al., U.S. Patent No. 5,681,746. In the June 26, 2002, Office Action (pages 2-3), the Examiner stated:

Applicants, Finer et al. (U.S. Patent 5,686,279, issued 11/11/97, see whole document, particularly Columns 10-11, 17, Claims 1-11) and Bodner et al. (U.S. Patent 5,681,746, issued 10/28/97, see whole document, particularly Columns 11-22) all recite packaging cell lines for propagating retroviral vectors independent of helper viruses, said viral vectors comprising a nucleic acid component and two different non-nucleic acid components wherein said two different non-nucleic acid components can be two different envelope proteins (one having a tropism for the packaging cell (which can be a murine cell) and one having a tropism for a different target cell (which can be from a different species, i.e. human, and can be an epithelial cell or marrow cell or T-cell, etc.)), said nucleic acid and non-nucleic acid components being capable of forming a complex (i.e. a viral particle) and wherein said nucleic acid sequences encoding said components can be stably integrated into the cell genome or can be present extra chromosomally. The nucleic acid component of the vector can be comprise sequences from two viruses that are native to the cell (i.e. encoding sequences for two different ecotropic or amphotropic

envelopes, etc.). Therefore, Finer et al. and Bodner et al. teach the claimed invention.

The anticipation rejection is respectfully traversed.

The present invention is directed to a packaging cell line for propagating a viral vector independent of a helper virus. The viral vector comprises a nucleic acid component and at least two different non-nucleic acid components. One of the non-nucleic acid components has a tropism for the cell line and the other non-nucleic acid component has a tropism for a target cell which is different from the cell line. The nucleic acid component and the non-nucleic acid components are capable of forming a specific complex or complexes, wherein the sequence or sequences for the viral vector nucleic acid component is stably integrated in the genome of the cell line. Furthermore, the sequence or sequences for the non-nucleic acid components of the viral vector are introduced into the packaging cell line by transient expression, episomal expression or stably integrated expression.

It is believed that neither Finer et al. nor Bodner et al. anticipate the present invention, particularly where the latter recites that "one of the non-nucleic acid components has a tropism for said cell line and the other non-nucleic acid component has a tropism for a target cell which is different from said cell line."

In further detail, Finer's '279 Patent describes using only one particular env protein that is selected from a group. This results in only a single tropism, although a variety of different tropisms may be selected. No mention is made of the desirability or utility for having more than one env gene in a vector particle. In Finer's '279 Patent, there is a reference to env proteins or combinations thereof in the claims, but in column 10, lines 19-22, it is revealed that combination refers to chimeric proteins i.e. a fusion of portions of two env genes to generate a single protein.

In the case of Bodner's '746 Patent, it is disclosed in column 19, lines 31-32 that "resultant viral particles contain more than one species of env protein." The context of column 19, lines 10- 46 begins, however, thusly:

Retroviral particles according to the invention may be directed towards a specific cell type by including in the retroviral particles a component, most frequently a polypeptide or carbohydrate, which binds to a cell surface receptor specific for that cell type.

Thus even when there is more than one species of env protein, the resultant viral particle in Bodner's disclosure is still directed towards a specific cell type.

Later sections in Bodner et al. make reference to chimeric molecules, but again, this reference is in the context of an ability to develop targeting to a specific cell type. Bodner et al. state in column 20, lines 14-16:

To accomplish this, the gene coding for the ligand can be functionally combined with the sequences coding for a membrane-associated domain.

In contrast to Bodner et al., the present invention comprises two tropisms and as such, it is not directed to a specific cell type. Instead, the present invention and packaging cell line is directed to at least two different cell types:

- a) the packaging cell line; and
- b) a target cell type that is different from the packaging cell line.

The Bodner references makes no reference as to the utility or the desirability for a tropism other than the target cell. Thus, the dual tropism recited in the present claims is altogether lacking in Bodner et al.

In view of the foregoing remarks and the lack of identity between the cited patents and their present claimed invention, Applicants respectfully request reconsideration and withdrawal of the anticipation rejection.

### **Commonality of Ownership**

Applicants acknowledge the Examiner's comments on page 3 regarding common ownership of the claims and invention. They confirm that the subject matter of the various claims was commonly owned at the time any inventions covered therein was made.

### **The First Rejection Under 35 U.S.C. §103**

Claims 83 and 85 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Finer et al.* or *Bodner et al.*, either in view of *Respass et al.*, U.S. Patent No. 6,013,517. In the Office Action (pages 4-5) the Examiner stated:

Applicants claim a packaging cell comprising a viral vector which encodes an antisense RNA targeted against a mRNA coding for an undesirable protein in a target cell.

*Fine et al.* and *Bodner et al.* are cited as in the above 35 USC 102(e) rejection of claims 75-82 and 88-90. Neither *Finer et al.* nor *Bodner et al.* teach expression of antisense sequences by viral vectors.

*Respass et al.* (U.S. Patent 6,013,517, issued 1/11/00, effective filing date 5/9/94, see whole document, particularly Columns 14-15, Claims 1, 8 and 11) recites the generation of packaging cell lines capable of generating retroviral vectors which are capable of expressing antisense RNAs complementary to undesirable mRNAs (i.e. mRNAs coding for cellular proteins required for cell growth in cancer cells) produced by target cells.

The ordinary skilled artisan, seeking to generate retroviral vector packaging cells capable of generating retroviral vectors capable of expressing an antisense sequence directed against the mRNA from an undesirable gene in a target cell, would have been motivated to combine the teachings of *Finer et al.* or *Bodner et al.* on the generation of retroviral packaging cells with the characteristics of claims 75-82 and 88-90 with the teachings of *Respass et al.* on the packaging cells which generate retroviral vectors capable of expressing antisense sequences targeted against mRNAs from undesirable genes in target cells because the expression of antisense sequences targeted against undesirable genes in target cells has been a well known techniques to

inhibit the growth of undesirable target cells or inhibit virus replication, etc. It would have been obvious for the ordinary skilled artisan to do this because use of viral (retroviral) vectors to deliver antisense sequences to target cells, in the context of treatment of diseases, was well known in the art (see Respass et al.) and was a standard use of retroviral vectors. Given the teachings of the cited prior art and the level of skill the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

The first obviousness rejection is respectfully traversed.

As indicated in the anticipation rejection above, neither Finer et al. nor Bodner et al. disclose the instantly claimed packaging cell line in two tropisms are present. Thus, even the addition of the Respass '517 Patent does not render Applicants' claimed invention obvious.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

### **The Second Rejection Under 35 U.S.C. §103**

Claim 84 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Finer et al. or Bodner et al., either in view of Bujard et al., U.S. Patent No. 6,271,348. In the Office Action (pages 5-6) the Examiner stated:

Applicants claim a viral packaging cell line wherein the viral vector produced expresses a polypeptide of interest and an antisense RNA in a target cell.

Finer et al. and Bodner et al. are cited as in the above 35 USC 102(e) rejection. Neither Finer et al. nor Bodner et al. teach a packaging cell line producing a viral vector which expresses a polypeptide of interest and an antisense sequence in a target cell.

Bujard et al. (U.S. Patent 6,271,348, issued 8/7/01, effective filing date 6/7/95, see whole document, particularly Columns 18 and 21-22) recites the use of bidirectional promoters in viral vectors

(which can be retroviral vectors) so that two gene products can be produced. The gene products can be two polypeptides of interest or two antisense sequences or a polypeptide and an antisense sequence.

The ordinary skilled artisan, seeking to generate a packaging cell line comprising a viral vector capable of expressing a polypeptide of interest and a antisense sequence in a target cell, would have been motivated to combine the teachings of Finer et al. or Bodner et al. with regard to the generation of packaging cell lines with the characteristics of claims 75-82 and 88-90 with the teachings of Bujard et al. on the use of viral vectors comprising bi-directional promoters for expression of multiple sequences encoding polypeptides and/or antisense sequences because the use of bi-directional promoters increases the versatility of viral vectors in that more than one sequence of interest can be expressed by a single vector. It would have been obvious for the ordinary skilled artisan to do this because being able to generate more versatile viral vectors capable of expressing two different sequences of interest would be desirable (See Bujard et al.). Given the teachings of the cited prior art and given the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

The second obviousness rejection is respectfully traversed.

As indicated above, the Finer et al. and Bodner et al. cited patents do not disclose a packaging cell line having two tropisms, unlike the instantly claimed invention. Thus, even the addition of Bujard's '348 Patent does not render the present invention obvious.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the second obviousness rejection.

### **The Third Rejection Under 35 U.S.C. §103**

Claims 83, 85, 86-87 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Finer et al.* or *Bodner et al.*, either in view of *Dietz et al.*, U.S. Patent No. 5,814,500. In the Office Action (pages 6-8) the Examiner stated:

Applicants claim a packaging cell line comprising a viral vector which encodes an antisense RNA targeted against a mRNA coding for an undesirable protein in a target cell and wherein the antisense RNA can be a part of a chimeric RNA molecule that comprises sequences from small nuclear RNAs (for example, U1 snRNA).

*Finer et al.* and *Bodner et al.* are cited as in the above 35 USC 102(e) rejection of claims 75-82 and 88-90. Neither *Finer et al.* nor *Bodner et al.* teach expression of antisense sequences by viral vectors.

*Dietz* (U.S. Patent 5,814,500, issued 9/29/98, filed 10/31/96, see whole document, particularly Columns 2-3, 8 and Claims 1-11) recites the use of retroviral vectors to express antisense sequences targeted against undesirable target genes and wherein the antisense RNA is part of a chimeric RNA molecule that comprises sequences from snRNAs (such as U1 snRNA).

The ordinary skilled artisan, seeking to develop packaging cell lines capable of generating retroviral vectors capable of expressing an antisense sequence or a chimeric antisense RNA molecule, would have been motivated to combine the teachings of *Finer et al.* or *Bodner et al.* on the generation of retroviral packaging cell lines with the characteristics of claims 75-82 and 88-90 with the teachings of *Dietz* concerning the use of retroviral vectors to express chimeric antisense sequences targeted against undesirable genes in target cells because the expression of antisense sequences targeted against undesirable genes was a well known technique in molecule biology and use of retroviral vectors to deliver chimeric RNAs to target cells was likewise known (*Dietz*). It would have been obvious for the ordinary skilled artisan to do this because delivery and expression of antisense sequences targeted against undesirable genes had been a well known (for almost two decades) technique in molecular biology. It would further have been obvious for the ordinary skilled artisan to select chimeric RNAs encoding antisense sequences and snRNAs because *Dietz* teaches that said chimeric RNAs make superior delivery vehicles for delivering the antisense sequences to the target cells. Given the

teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

The third obviousness rejection is respectfully traversed.

As also indicated above, Finer's and Bodner's cited U.S. patents do not disclose the instantly claimed packaging cell line wherein one of the non-nucleic acid components has a tropism for a cell line and the other non-nucleic acid component has a tropism for a target cell which is different from the cell line. Lacking the two tropisms of the presently claimed invention, Finer et al. and Bodner et al. cannot be supplemented by the Dietz '500 Patent to render the instant claims obvious.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the third obviousness rejection.

#### **The Rejection Under 35 U.S.C. §112**

Claim 88-90 stand rejected under 35 U.S.C. §112, second paragraph for indefiniteness. In the Office Action (pages 8) the Examiner stated:

Claims 88-90 are vague in the recitation of the phrase "virus that is native to" the cell line or target cell. It is unclear if this phrase means that the virus naturally infects and replicates within the cell or that the virus can infect the cell but not replicate in the cell, or that the virus genome is present in the cell but it is not replicated, etc.

The indefiniteness rejection is respectfully traversed.

As indicated in the opening remarks of this paper, claims 88-90 have been amended to remove the term "native" and replace it with reference to "tropism." It

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is believed, therefore, that these amendments render this ground of rejection moot and irrelevant.

Reconsideration and withdrawal of the rejection under §112, second paragraph, is respectfully requested.

Favorable action on this application is believed to be in order.

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Page 15 [Amendment Under 37 C.F.R. §1.116 (In Response To The  
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### SUMMARY AND CONCLUSIONS

Claims 75-90 continue to be presented for further examination. Of these, claims 75 and 88-90 have been amended. No other claims have been changed, canceled or added by this paper.

No fee or fees are believed to be due in connection with this Amendment or the accompanying filings. If any other fee or fees are due, however, for either this response or the accompanying filings, The Patent and Trademark is authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, and to credit any overpayment thereto.

Applicants respectfully submit that all of the instant claims are in allowable condition. Should it be deemed helpful or necessary, the Examiner is respectfully invited to telephone the undersigned at (212) 583-0100 to discuss the subject application.

Respectfully submitted,



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